Title: Efficacy and safety of long-acting beta agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis.

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What is the key question?

Do greater improvements of lung function with long-acting beta agonist/long-acting muscarinic antagonist (LABA/LAMA) combinations translate into better clinical benefits compared with monotherapies in stable COPD patients?

What is the bottom line?

The combination therapy was the most effective strategy in improving lung function, quality of life, symptom scores, and moderate-to-severe exacerbation rates and had similar effects on safety outcomes and severe exacerbations as compared with monotherapies.

Why read on?

Our systematic review summarizes the efficacy and safety of LABA/LAMA combination therapy in patients with moderate-to-severe COPD and describes the limitations of the current data.

ABSTRACT

Background: The place of long-acting beta agonist/long-acting muscarinic antagonist (LABA/LAMA) combinations in stable COPD patients is not well defined. The purpose of this study was to systematically review the efficacy and safety of LABA/LAMA combinations.

Methods: Several databases and manufacturers' website were searched for relevant clinical trials. Randomized control trials, at least 12 weeks duration, comparing a LABA/LAMA combination with placebo and/or monotherapy were included. The data were pooled using a network as well as a traditional direct comparison meta-analysis.

Results: Twenty three trials with a total of 27,172 patients were included in the analysis. LABA/LAMA combinations were associated with a greater improvement in lung function, St. George's Respiratory Questionnaire (SGRQ) score, and Transitional Dyspnea (TDI) Index than monotherapies. LABA/LAMA combinations were associated with a significantly greater proportion of SGRQ and TDI responders than monotherapies (odds ratio (OR) 1.23 [95% credible interval (CrI) 1.06-1.39], OR 1.34 [95% CrI 1.19-1.50] vs. LABAs and OR 1.24 [95% CrI 1.11-1.36], OR 1.31 [95% CrI 1.18-1.46] vs. LAMAs respectively) and fewer moderate-to-severe exacerbations compared with LABAs (hazard ratio (HR) 0.82 [95% CrI 0.73-0.93]), but not when compared with LAMAs (HR 0.92 [95% CrI 0.84-1.00]). There were no statistically significant differences associated with LABA/LAMA combinations compared with monotherapies in safety outcomes as well as in severe exacerbations.

Conclusion: The combination therapy was the most effective strategy in improving lung function, quality of life, symptom scores, and moderate-to-severe exacerbation rates and had similar effects on safety outcomes and severe exacerbations as compared with monotherapies.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) will likely become the third leading cause of death by 2030 according to World Health Organization and continues to be a major cause of disability and rising health care costs worldwide.[1] The total cost of COPD in 2010 was $49.9 billion, including health care expenditures of $29.5 billion in direct health care costs, $8.0 billion in indirect morbidity costs, and $12.4 billion in indirect mortality costs in the United States.[2] These costs were the highest among common lung diseases.

Current guidelines developed by Global Initiative for COPD (GOLD) recommend a maintenance therapy either with a long-acting muscarinic antagonist (LAMA) or a long-acting beta agonist (LABA) in symptomatic patients with moderate or more severe COPD.[3] When patients are not adequately controlled with a single long-acting bronchodilator, combining a LAMA with a LABA may be beneficial.[4]

European and Japanese regulatory agencies recently approved a once-daily fixed-dose combination of indacaterol and glycopyrronium as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. A fixed-dose combination of umeclidinium/vilanterol was approved in the United States and Canada for maintenance treatment of COPD.[5] Although LABA/LAMA combination therapies were superior to monotherapies with regard to lung function improvement, it is less clear that the surplus of bronchodilation by combination therapy would translate into better clinical outcomes such as better quality of life and fewer exacerbations.[6, 7]

The purpose of this study was to systematically review the efficacy and safety of LABA/LAMA combinations in COPD from randomized controlled trials with a network meta-analysis as well as with a traditional direct comparison meta-analysis. When no clinical trials exist that directly compare all relevant treatment options, indirect comparisons can be made by comparing the relative effects of treatments against a common comparator or combining a variety of comparisons that taken together from one or more chains linking the treatments of interest (variously referred to as a multiple treatment comparison or network meta-analysis (NMA)).[8]

Methods

Identification of trials and data extraction

We identified all relevant clinical trials which evaluated clinical efficacies and safety of a LABA/LAMA combination in stable COPD patients without an acute or recent exacerbation. Two authors (YO, STS) independently searched the Ovid Medline database for studies published from 1946 to May 21, 2015 using the MeSH headings and keywords: randomized controlled trial AND Pulmonary Disease, Chronic Obstructive AND aclidinium, glycopyrronium, or tiotropium AND formoterol, indacaterol, olodaterol, salmeterol, or vilanterol OR QVA149. In addition, we searched Scopus, CINAHL, and the internet including the online trial registries of manufacturers of the above mentioned fixed-dose LABA/LAMA products. Bibliographies of all selected articles and review articles which included information on a LABA/LAMA combination in COPD were also reviewed for other relevant articles. We included any randomized clinical trial, published or unpublished, evaluating COPD patients with a LABA/LAMA combination. Randomized control trials had to be of at least 12 weeks duration. A control intervention had to include a placebo, a LABA, or a LAMA. We chose change from baseline (CFB) in trough forced expiratory volume in 1 second (FEV1) in liter, Transitional Dyspnea Index (TDI), CFB in St. George's Respiratory Questionnaire (SGRQ), a proportion of SGRQ and TDI responders (defined as a subject with an improvement of at least four units in SGRQ total score or one unit in TDI score),[9] COPD exacerbations, mortality, total serious adverse events (SAEs), cardiac SAEs, and dropouts due to adverse event, as the outcome assessment criteria for the purpose of our meta-analysis.

Two authors (YO, STS) independently screened studies by title and abstract to evaluate whether a trial met the inclusion criteria. We extracted data on COPD exacerbations as moderate and severe. Moderate was generally defined as "worsening respiratory status which required treatment with systemic corticosteroids and/or antibiotics" and severe as "rapid deterioration which required hospitalization." Data were abstracted on study design, study size, population, severity of illness, and the impact of a LABA/LAMA combination on the end points of interest. The risk of bias was assessed with the following items: (1) adequacy of sequence generation, (2) allocation concealment, (3) blinding of participants and investigators, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and other bias.[10] Disagreements regarding values or analyses were resolved by discussion.

Statistical analysis

The primary analyses were NMAs using a Bayesian Markov chain Monte Carlo (MCMC) method and fitted in WinBUGS version 1.4.3(Medical Research Council Biostatistics Unit, Cambridge, UK) using code adapted from Dias et al, which correctly accounts for correlations in trials with more than two arms.[11] In a Bayesian analysis, a prior distribution of a parameter is the probability distribution that represents uncertainty about the parameter before the current data are examined. Current data and assumptions concerning how they were generated are summarized in the likelihood. Combining the prior distribution and the likelihood functions leads to the posterior distribution of the parameter which is used for inference. This distribution will be summarized by its median and 95% credible interval (CrI). Crls are the Bayesian equivalent of classical confidence intervals, but they are interpreted as defining the probability (usually 95%) that the relative treatment effects lie between its bounds. NMA estimates the comparative efficacy between all treatments, including those that have not been directly compared by including all relevant evidence (direct and indirect), and provide the most flexible approach to indirect comparison modeling. For the analyses in WinBUGS, inference was based on 100,000 iterations of MCMC with an initial burn-in period of 50,000 iterations.[12]

A data structure table was constructed to choose an optimal model for each outcome (Table S1 in Online Supplement). Model selection and its rationale are summarized in the Table S2 in Online Supplement. Each pair of treatments was compared by estimating an odds ratio (OR) or hazard ratio (HR) for a dichotomous outcome and a difference in mean or median for a continuous outcome. Treatment baselines and effects were given vague normal priors with mean 0 and variance 10,000 and between-trials standard deviations (SDs) were given uniform distribution with lower bound 0 and upper bound 5. The upper bound of 5 was thought to be sufficiently large for outcomes on a log scale. The posterior distribution was examined to ensure it was sufficiently different from the prior and that the prior was therefore not having undue influence on the resulting posterior.

The probability that each intervention arm was associated with being the most efficacious was calculated by counting the proportion of iterations of the Markov chain in which each intervention arm had the highest HR, OR, or mean difference (MD). The surface under the cumulative ranking (SUCRA), which is a simple numerical summary of these probabilities, was also calculated. The SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst.[13]

Assessment of model fit was based on comparison of residual deviance to the number of unconstrained data points, and between-study SD. We compared fixed and random effects models using the Deviance Information Criterion (DIC), a measure of model fit that penalizes model complexity. The model with lower values on the DIC was preferred, with differences of three or more units considered meaningful.[14] If two models had a similar DIC, a fixed-effects model was preferred unless there was heterogeneity in the pairwise comparison, in which case a

random-effects model was used. Inconsistency was assessed by comparing the model fit and between-study heterogeneity from the NMA models with those from an unrelated effects (inconsistency) model.[15]

The presence of heterogeneity was assessed by comparing a between-trials SD to the size of the relative treatment effects, on log-scale for OR and HR. If the between-trials SD approximates the size of treatment effect, heterogeneity is likely very high so that results from a future trial could include zero or even harmful effects. Heterogeneity was further explored by fitting covariates (i.e., FEV1 at baseline, treatment duration (a minimum of 6 months), publication status (published vs. unpublished) and smoking status) in a meta-regression analysis.[16] A subgroup interaction model was used for the treatment duration and a continuous covariate model was used for the rest of covariates.

We conducted traditional pairwise meta-analyses, considering only direct evidence comparing the combination therapy with monotherapies or placebo using the same outcome variables. For the pairwise meta-analysis, we tested heterogeneity between trials with I^2 statistic with I^2 >50% indicating significant heterogeneity. A random effects model (DerSimonian-Laird) was used if significant heterogeneity was detected. A fixed-effects model was used otherwise. Haldane correction was applied by adding 0.5 to each count when a data set contained zero in any cell to make a calculation possible for the main effect or variance.[17] Results from our network meta-analysis were qualitatively compared with direct pairwise estimates. The data analysis was performed using meta-analysis software (StatsDirect 2.7.8, StatsDirect Ltd, Cheshire UK).

Sample size calculations and power analyses were conducted for clinically relevant outcomes such as SGRQ and TDI responders and COPD exacerbations with a method described by Thorlund and Mills.[18] A required sample size was calculated by applying a mean event rate of the comparator arm from the included trials, a type I error of 5%, and a power of 90%, expecting to detect an additional 20% relative efficacy with the combination arm. Heterogeneity was estimated from I^2 index of a head-to-head comparison and used for correcting the sample sizes.

RESULTS

Study Selection

The electronic database searches identified 112 citations. Ninety seven studies were excluded on abstract review. The remaining 15 studies were reviewed for further details. Additional 5 studies were excluded for various reasons as shown in Figure 1. Further search on manufactures' website and internet identified 10 additional studies including 3 unpublished studies. We included 23 trials from 20 reports with a total of 27,172 randomized patients.[19-38] The study and patient characteristics are presented in Table 1.

Study, year	No. of patients†	Duration of treatment (weeks)	Treatment comparisons	Mean age	Male %	Current smoker %	Baseline FEV1 % §	Baseline FEV1 (L) ≠
Buhl 2015 [19]	5162	52	TIO/OLO 5/5 mcg TIO/OLO 2.5/5 mcg TIO 5 mcg TIO 2.5 mcg OLO 5 mcg	64.0	73	37	50.0	1.17
Celli 2014 [20]	1489	24	UMEC/VI 125/25 mcg UMEC 125 mcg VI 25 mcg Placebo	62.9	65	52	48.2	1.28
Decramer 2014a [21]	843	24	UMEC/VI 125/25 mcg	62.9	69	51	47.7	1.31

			UMEC/VI 62.5/25 mcg VI 25 mcg TIO 18 mcg					
Decramer 2014b [21]	869	24	UMEC/VI 125/25 mcg UMEC/VI 62.5/25 mcg UMEC 125 mcg TIO 18 mcg	64.6	68	45	47.1	1.16
D'Urzo 2014 [22]	1669	24	ACL/FM 400/12 mcg ACL/FM 400/6 mcg ACL 400 mcg FM 12 mcg Placebo	63.9	53	52	53.5	1.36
Donohue 2014 [31]	562	52	UMEC/VI 125/25 mcg UMEC 125 mcg Placebo	61.3	67	63	54.7	1.49
Maleki-Yazdi 2014 [23]	905	24	UMEC/VI 62.5/25 mcg TIO 18 mcg	62.3	68	57	46.3	1.41 §
Singh 2014 [24]	1729	24	ACL/FM 400/12 mcg ACL/FM 400/6 mcg ACL 400 mcg FM 12 mcg Placebo	63.2	68	47	54.3	1.41
Vincken 2014 [25]	447	12	IND/Glyco 110/50 mcg IND 150 mcg	63.6	81	42	54.9	1.46
ZuWallack 2014* (ANHELTO 1 & 2) [26]	2267	12	TIO/OLO 18/5 mcg TIO 18 mcg	64.3	52	49	53.7	1.25
Bateman 2013 [27]	2135	26	IND/Glyco 110/50 mcg IND 150 mcg Glyco 50 mcg TIO 18 mcg Placebo	63.9	75	40	55.2	1.30
Dahl 2013 [28]	338	52	IND/Glyco 110/50 mcg Placebo	62.6	77	45	57.4	1.45
Donohue 2013 [29]	1532	24	UMEC/VI 62.5/25 mcg UMEC 62.5 mcg VI 25 mcg Placebo	63.1	71	50	47.4	1.23
Wedzicha 2013 [30]	2205	64	IND/Glyco 110/50 mcg Glyco 50 mcg TIO 18 mcg	63.3	75	38	37.2	0.90
DB2114417 2012 [32]	641	12	UMEC/VI 125/25 mcg UMEC/VI 62.5/25 mcg VI 25 mcg UMEC 125 mcg UMEC 62.5 mcg Placebo	61.6	56	63	NR	1.44
DB2114418 2012 [33]	554	12	UMEC/VI 125/25 mcg UMEC/VI 62.5/25 mcg VI 25 mcg UMEC 125 mcg UMEC 62.5 mcg Placebo	62.6	55	61	NR	1.32
Mahler 2012a [34]	1131	12	TIO 18 mcg /IND 150 mcg TIO 18 mcg	63.7	69	38	48.6	1.15
Mahler 2012b [34]	1142	12	TIO 18 mcg /IND 150 mcg TIO 18 mcg	63	66	40	48.6	1.14
Novartis A1301 2012 [35]	158	52	IND/Glyco 110/50 mcg TIO 18 mcg	69.3	96	NR	NR	1.33 ¶
Tashkin 2009 [36]	243	12	TIO 18 mcg /FM 12 mcg TIO 18 mcg	63.9	66	47	NR	NR
Vogelmeier 2008 [37]	847	24	TIO 18 mcg /FM 10 mcg FM 10 mcg TIO 18 mcg Placebo	62.6	78	NR	51	1.5
Aaron 2007 [38]	304	52	TIO 18 mcg /SAL 50 mcg TIO 18 mcg	67.9	56	26	41.7	1.01

Table 1. Study characteristics of included trials. ACL = aclidinium; FEV1= forced expiratory volume in 1 second; FM=formoterol; Glyco= glycopyrronium; IND= indacaterol; NR= not reported; OLO= olodaterol; SAL=salmeterol; TIO= tiotropium; UMEC= umeclidinium; VI=vilanterol † Number of patients included in this analysis § post-bronchodilator ≠ pre-bronchodilator ¶ at week 3 * includes 2 trials making a total of 23 trials.

Formoterol, indacaterol, olodaterol, salmeterol, and vilanterol were grouped as LABA and aclidinium, glycopyrronium, umeclidinium, and tiotropium were grouped as LAMA. The mean age ranged from 61.3 to 69.3 years. The proportion of male patients and current smokers ranged from 52% to 96% and 26% to 63%. The mean baseline FEV1 ranged from 0.90 to 1.5 liters. FEV1 percent predicted ranged from 37.2% to 57.4 %. The network of treatments is displayed in Figure 2. The treatments formed a closed network, which was amenable to a network meta-analysis.

Methodological quality of included studies

Generally, the risk of bias in the included studies was deemed moderate to low. Allocation concealment was appropriate in 16 studies, and unclear in 3 studies. All trials presented intention-to-treat analyses except for two trials which excluded two patients out of 1134 and 1137 patients who did not receive the study treatment.[26] Nineteen studies were double blinded (Table S3 in Online Supplement). In the opinion of the authors, there were no studies that clearly should have been excluded from the analysis because of differences in baseline characteristics or poor quality.

Consistency assessment (Similarity of participants, interventions and trial methodology)

All trials were consistent in their key inclusion and exclusion criteria (Table S4 in Online Supplement). All studies recruited patient with aged > 35-40 years with a diagnosis of COPD in accordance with American Thoracic Society-European Respiratory Society or GOLD guidelines, at least 10 pack year of smoking history, and moderate or severe disease with FEV1 of ranging 30 to 70 percent of predicted. Patients with asthma, and other respiratory or cardiovascular disease were excluded in all trials. The concomitant use of a fixed dose of inhaled corticosteroids (ICS) was allowed in most studies, prohibited in two studies [26, 38], and unclear in one study [35] which was addressed in a sensitivity analysis. A recent COPD exacerbation within a month of study entry was usually excluded from the study. Baseline characteristics of studied patients were similar in all included studies (Table 1) as well as in class pair-wise comparisons (e.g. LABA vs. combination, LAMA vs. placebo. Table S5 in Online Supplement). Baseline FEV1 was somehow lower in the combination vs. LAMA comparison, but summary baseline characteristics were comparable across pair-wise comparisons between classes. Trial duration varied across studies which was addressed by including only data relevant to the time points specified or by modelling the data as hazards with the binominal-cloglog model which allows for the different follow-up time. In general, characteristics of participants, interventions and trial methodology were fairly comparable in all studies and across pairwise comparisons, and therefore we found nothing to suggest that the consistency assumption may not hold.

Network meta-analysis

The clinical trials were synthesized with a network meta-analysis. The individual study results are presented in Table S6-8 in Online Supplement. The autocorrelation plots showed that throughout the iterative process the autocorrelation was satisfactorily reduced to a nominal amount and the Brooks-Gelman-Rubin plots showed that the model had converged satisfactorily.[39] When examining outcome measures, a fixed-effects model showed largely similar DIC values and results as a random-effects model. A random-effects model was chosen in all

outcomes according to our prespecified selection criteria except for CFB in SGQR at 3 months, TDI, proportion of TDI responders, severe exacerbations, mortality, and total SAEs. The between study heterogeneity and DICs were similar between the NMA and inconsistency models suggesting no evidence of inconsistency in the network, although this should be interpreted with caution as there may not be sufficient power to detect inconsistency. Ranking results of each outcome are presented in Table 2.

	Probability of being the best therapy	SUCRA value	Median ranking [95% CrI]
Treatment	Change from baseline in FEV1 (L) - 3 months		
Placebo	0%	0%	4[4-4]
LABA	0%	33.4%	3[3-3]
LAMA	0%	66.6%	2[2-2]
LABA/LAMA	100%	100%	1[1-1]
Treatment	Change from baseline in FEV1 (L) - 6 months		
Placebo	0%	0%	4[4-4]
LABA	0%	33.6%	3[3-3]
LAMA	0%	66.4%	2[2-2]
LABA/LAMA	100%	100%	1[1-1]
	Change from baseline in FEV1 (L) - 12 months		
Placebo	0.1%	0.5%	3[3-3]
LABA	N/A	N/A	N/A
LAMA	2.1%	50.7%	2[2-2]
LABA/LAMA	97.7%	98.8%	1[1-1]
	Change from baseline in SGRQ – 3 months		
Placebo	0%	0%	4[4-4]
LABA	0%	49.0%	2[2-3]
LAMA	0%	51.0%	3[2-3]
LAMA/LABA	100%	100%	1[1-1]
	Change from baseline in SGRQ – 6 months		
Placebo	0%	0.1%	4[4-4]
LABA	0.6%	52.2%	2[2-3]
LAMA	0.1%	47.9%	3[2-3]
LAMA/LABA	99.2%	99.7%	1[1-2]
	SGRQ responder† – 6 months		
Placebo	0%	0.4%	4[4-4]
LABA	0.4%	67.2%	2[2-3]
LAMA	0%	36.8%	3[2-3]
LAMA/LABA	99.5%	95.6%	1[1-2]
	Transitional Dyspnea Index – 3 months		
Placebo	0%	0%	4[4-4]
LABA	0%	55.7%	2[2-3]
LAMA	0%	44.3%	3[2-3]
LABA/LAMA	99.9%	100%	1[1-1]
	Transitional Dyspnea Index – 6 months		
Placebo	0%	0%	4[4-4]
LABA	0%	43.0%	3[2-3]
LAMA	0%	57.0%	2[2-3]
LABA/LAMA	99.4%	100%	1[1-1]
	TDI responder* – 6 months		
Placebo	0%	0%	4[4-4]
LABA	0%	44.2%	3[2-3]
LAMA	0.1%	55.8%	2[2-3]
LABA/LAMA	99.9%	100%	1[1-1]
	Moderate-to-severe exacerbations		
Placebo	0%	2.6%	4[4-4]
LABA	0.2%	34.3%	3[2-3]
LAMA	2.9%	66.5%	2[1-3]
LAMA/LABA	97.0%	99.0%	1[1-2]
	Severe exacerbations		
Placebo	4.6%	10.2%	4[1-4]
LABA	37.4%	66.0%	2[1-4]
LAMA	7.5%	44.8%	3[1-4]
LAMA/LABA	50.5%	79.0%	1[1-3]
	Mortality		

Placebo	84.8%	91.4%	1[1-4]
LABA	7.6%	41.3%	3[1-4]
LAMA	0.6%	14.5%	4[2-4]
LAMA/LABA	7.1%	52.7%	3[1-4]
	Total serious adverse events		
Placebo	62.7%	76.4%	1[1-4]
LABA	6.6%	23.6%	4[1-4]
LAMA	26.0%	64.7%	2[1-4]
LAMA/LABA	4.7%	35.2%	3[1-4]
	Cardiac serious adverse events		
Placebo	89.6%	94.7%	1[1-3]
LABA	2.1%	22.3%	4[2-4]
LAMA	1.6%	28.3%	3[2-4]
LAMA/LABA	6.7%	54.6%	2[1-4]
	Dropout due to adverse event		
Placebo	22.7%	42.8%	3[1-4]
LABA	11.7%	29.6%	3[1-4]
LAMA	42.0%	70.0%	2[1-4]
LAMA/LABA	23.5%	57.6%	2[1-4]

Table 2. Probability of best therapy, SUCRA values and ranking of therapy. *defined as a subject with a TDI score of one unit or more. †defined as a subject with a SGRQ score of 4 units below baseline or lower. CFB=change from baseline; CrI= credible interval; FEV1= forced expiratory volume in 1 second; LABA= long-acting beta-agonist; LAMA=long-acting muscarinic antagonist; N/A= not applicable; SGRQ=St. George's Respiratory Questionnaire; SUCRA= surface under the cumulative ranking curve; TDI= Transitional Dyspnea Index.

Forced expiratory volume in 1 second (FEV1)

Trough FEV1 data were available in 13, 12 and 4 trials at 3, 6, and 12 months (n=12224, 16065, and 4836 respectively). Improvement in trough FEV1 to the end of the trials was greater with LABA/LAMA combinations than with placebo, LABAs or LAMAs at all time points. LABA/LAMA combinations were ranked first [95% CrI 1-1] at all time points, with a mean improvement over placebo of 201ml [95% CrI 172, 230] to 243ml [95% CrI 139, 351]. LAMAs and LABAs were ranked second and third with the MDs of 64ml [95%CrI 51, 78] to 73ml [95% CrI 43, 149] and 95ml [95% CrI 71, 117] to 104ml [95% CrI 84, 126] compared with LABA/LAMA combinations. Class differences did not appear significantly different at 3, 6 and 12 months, except for LABAs at 12 months at which time point data were not available. (Fig. 3) Wider 95% CrIs were observed at 12 months as the number of included studies decreased.

Health related quality of life and symptom scales (SGRQ and TDI scores and responders)

The data for CFB in SGRQ and TDI were available in 9 and 6 trials at 3 months and 9 and 8 trials at 6 months (n= 12042, 7315, 12716, and 14568 respectively). The data for SGRQ and TDI responders at 6 months were available in 12 and 7 trials (n=18,536 and 9,045 respectively). The combination therapy was ranked highest, followed by LABAs and LAMAs in all SGRQ outcomes. The efficacy of combination therapy in CFB in SGRQ was less prominent at 6 months as compared with 3 months, especially with LABAs (MD -4.6 [95% CrI -5.9, -3.3], -2.3 [95% CrI -3.3, -1.3], and -2.3 [95% CrI -2.9, -1.7] for placebo, LABAs and LAMAs respectively at 3 months and -4.1 (95% CrI -5.9, -2.3), -1.1 (95% CrI -2.5, 0.4), and -1.6 (95% CrI -2.8, -0.5) at 6 months Fig. 4A). Although the MD and its 95% CrI between combination therapy and monotherapies did not reach the minimum clinically important difference of 4 points in SGRQ score, LAMA/LABA combinations were associated with a significantly greater proportion of SGRQ responders compared with LAMAs and LABAs (OR 1.23 [95% CrI 1.06, 1.39] and1.24 [95% CrI 1.11, 1.36] respectively Fig. 5).

As for TDI, the combination therapy was ranked highest, followed by LABAs or LAMAs. The combination therapy yielded a significant improvement in TDI score compared with placebo, LABAs and LAMAs at 3 months (MD 1.21 [95% CrI 0.95, 1.48], 0.37 [95% CrI 0.16, 0.57], and 0.41 [95% CrI 0.23, 0.59] respectively). The class differences remained constant and statistically significant at 6 months (Fig. 4B). Although the MD and its 95% CrI between combination therapy and monotherapies did not reach the minimum clinically important difference of 1 point in TDI, LAMA/LABA combinations were associated with a significantly greater proportion of TDI responders compared with LAMAs and LABAs (OR 1.34 [95% CrI 1.16, 1.56] and 1.30 [95% CrI 1.13, 1.48] respectively Fig. 5). The 95% CrIs of ranking suggested that only combination therapy could be ranked first in all SGRQ and TDI outcomes (Table 2).

COPD exacerbations

COPD exacerbation data were available in 16 trials (n=18,224) for moderate-to-severe exacerbations and in 19 trials (n=25,401) for severe exacerbations. LABA/LAMA combinations were ranked first and second for the prevention of moderate-to-severe and severe exacerbations with a probability of being the best therapy of 97.0% and 30.2% respectively. The combination therapy was associated with significantly fewer moderate-to-severe exacerbations compared with placebo and LABAs (HR 0.66[95% CrI 0.57, 0.77], 0.82 [95% CrI 0.73, 0.93] respectively), but not when compared with LAMAs (HR 0.92 [95%CrI 0.84, 1.00]). LAMAs had a median rank of two in preventing moderate-to-severe exacerbations and the 95% CrI suggested that they could also be ranked first, second, or third (median ranking 2 [95%CrI 1-3]). There were no significant differences in severe exacerbations associated with LABA/LAMA combinations compared with placebo, LABAs, or LAMAs and there was a large degree of overlap in ranking (Fig. 6 and Table 2).

Adverse events

The results of safety outcomes are presented in Table 3. There were no significant differences in mortality, total SAEs, or dropouts due to adverse event among all comparators (Table 3).

	Mortality FE HR (95%CrI)	Total SAEs FE HR (95%CrI)	Cardiac SAEs RE HR (95%CrI)	Dropouts due to AE RE HR (95%CrI)
No. of studies	15	20	16	16
No. of patients	24,041	27,172	25,913	23,529
vs. placebo	1.95 (0.73, 7.71)	1.10 (0.89, 1.38)	1.65 (0.81, 3.35)	0.95 (0.71, 1.28)
vs. LABA	0.99 (0.61, 1.66)	0.96 (0.84, 1.10)	0.82 (0.46, 1.35)	0.92 (0.72, 1.19)
vs. LAMA	0.87 (0.64, 1.16)	1.04 (0.95, 1.14)	0.87 (0.59, 1.27)	1.03 (0.84, 1.26)

Table 3. Summary effects of LABA/LAMA combinations versus comparators on adverse events. Note: Abbreviations: AE=adverse event; CrI=credible interval; FE= fixed-effects; HR= hazard ratio; LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; RE= random-effects; SAE=serious adverse event.

There was considerable overlap in credible intervals and rankings. Any arm including placebo could be ranked as the best therapy in all safety outcomes except for LAMAs in mortality and cardiac SAEs and LABAs in cardiac SAEs. Placebo was ranked highest in mortality, total SAEs, and cardiac SAEs. LABA/LAMA combinations were ranked second in mortality, cardiac SAEs, and dropouts due to adverse event, but again, there was a large degree of overlap (Table 3).**Assessment of consistency and exploration of heterogeneity**

The between-trials SDs were relatively large compared with the relative treatment effects in severe exacerbations, mortality, total SAEs, cardiac SAEs and dropouts due to adverse event (Table S9 in Online Supplement). The meta-regression adjustment for the proportion of active smokers, FEV1 at baseline, study duration (a minimum of 6

months), and publication status (published vs. unpublished) did not alter the main findings. Between-trials heterogeneity was either unchanged, increased, or only slightly reduced with the introduction of those covariates. Comparisons between network and direct pairwise meta-analyses were similar in magnitude and direction of effect estimates, with the exception of the combination vs. LAMA comparison in moderate-to-severe exacerbations and the combination vs. LAMA comparison in dropouts due to adverse event. However, these inconsistencies did not alter the main findings (Table S10 in Online Supplement). Two studies included a randomly assigned group that received tiotropium as an open-label treatment.[30, 37] The concomitant use of ICS was prohibited in two studies[26, 38] and unclear in one study.[30] We performed a sensitivity analysis excluding these studies and the results were essentially unchanged.

Power analyses and sample size calculations

The heterogeneity-corrected effective total sample size for the SGRQ and TDI responders and moderate-to-severe exacerbations was greater than the required sample size to detect additional 20% relative efficacy with a power of 90% (Table S11 in Online Supplement). Statistical power for combination therapy vs. comparators were 95% or greater in those outcomes. On the other hand, the effective total sample size for severe exacerbations was substantially smaller than the required sample size except for the combination therapy vs. LAMA comparison. Statistical power estimates for the combination therapy vs. placebo, LABA and LAMA comparisons were 29.8%, 55.5%, and 93.5% respectively in severe exacerbations.

DISCUSSION

Our systematic review of the currently available randomized trials of LABA/LAMA combinations for stable COPD demonstrated that LABA/LAMA combinations yielded a greater improvement in trough FEV1, and SGRQ and TDI scores than monotherapies. The ranking statistics demonstrated that combination therapy was the most effective strategy in improving lung function, quality of life and symptom scores as well as in reducing moderate-to-severe exacerbations. The combination therapy was associated with a significantly greater proportion of SGRQ and TDI responders than monotherapies. The combination therapy was ranked highest in reducing moderate-to-severe exacerbations and was associated with significantly fewer exacerbations than LABAs, but not when compared with LAMAs. LAMAs could also be ranked first in reducing moderate-to-severe exacerbations. There were no statistically significant differences among all comparators in severe exacerbations or safety outcomes, including mortality, total SAEs, cardiac SAEs, and dropouts due to adverse event. The sample size analysis suggested that the analyses for severe exacerbations were underpowered except for the combination vs. LAMA comparison. The sample size for SGRQ and TDI responders and moderate-to-severe exacerbations appeared adequate.

The results of our analysis are in line with a previous meta-analysis which demonstrated tiotropium/LABA combinations were associated with a small increase in lung function and a statistically significant improvement in quality of life compared with tiotropium alone. Improvement in other secondary outcomes, such as COPD exacerbations and SAEs was similar between both groups.[40] It is not surprising that dual therapies were not associated with significantly fewer exacerbations compared with LAMAs in the current analysis given that the concomitant use of LABA did not enhance the efficacy of LAMAs in reducing COPD exacerbations in a recent meta-regression analysis. [41] A similar phenomenon was observed among short-acting bronchodilators. Only ipratropium containing arms had reduced COPD exacerbations and adding albuterol to ipratropium did not reduce COPD exacerbations compared with ipratropium alone.[42] It was speculated that alterations in mucus production, rheology by glands, or mucus clearance in small airways were primarily responsible for COPD exacerbations which

were favorably affected by anticholinergics rather than by beta-2 agonists. The above notion is further supported by the current analysis with the strength of the NMA, which is the correct inclusion of multi-arm trials, of which this network had many, including several studies comparing all four interventions.

It is important to note the limitations of our study. First, heterogeneity was observed in both pairwise and network meta-analyses. None of the trial-level covariates we assessed explained the heterogeneity. Patient and study characteristics of the included studies were relatively homogenous, but between-trial comparisons are known to be vulnerable to ecologic bias.[13] The subgroup analysis to assess biases by systematic differences between studies was also compromised due to limited information. For example, the proportion of current smokers and baseline pre-bronchodilator FEV1 values were not available in a few studies included in this analysis (Table 1). Individual patient data would be necessary to avoid ecological bias and gain a much greater statistical power to detect a true covariate effect. Other effect modifies including body mass index, Medical Research Council dyspnea score, exercise capacity (six-minute walk distance), presence of emphysema on chest computed tomography and cardiac comorbidities may have influenced the study results. Second, as with all meta-analyses, we are limited by the amount of evidence that is published, consequently some of the analyses may fail to detect a true treatment effect. Our sample size calculation suggested that the assessment of severe exacerbations was significantly underpowered except for the combination vs. LAMA comparison (Table S11 in the Online Supplement). Future studies enrolling patients at much higher risk for COPD exacerbations would be helpful to increase the statistical power and shed further light on the efficacy of LABA/LAMA combinations on severe exacerbations. An imbalance in study and patient characteristics across trials cannot be completely excluded as with all meta-analyses because patients are not randomized to different trials and randomization would not hold across the set of trials used for the analysis. The results were unchanged when adjusted for study level covariates, but the risk of residual confounding bias from unknown or unmeasured effect modifiers cannot be excluded.[43] However, it is unlikely that the results are substantially biased given the consistency of results between network and direct comparison meta-analyses and the purpose of our evidence synthesis is to provide an estimate, and its uncertainty, based on the current available evidence. Third, the data included in the network meta-analysis was extracted from randomized trials and the results may not be generalizable to all patients with COPD. Forth, a cost analysis was not conducted. Future studies, especially ones that compares LABA/LAMA, LABA/ICS, and LABA/LAMA/ICS combinations are necessary to determine the most cost-effective treatment option.

CONCLUSIONS

Our network analysis demonstrated that the combination therapy was the most effective strategy in improving lung function, quality of life, symptom scores, and moderate-to-severe exacerbation rates. The combination therapy was associated with fewer moderate-to-severe exacerbations compared with LABAs, but not when compared with LAMAs. The combination therapy had similar effects on safety outcomes and severe exacerbations as compared with monotherapies. Future studies including patients with a more severe form of COPD and comparing LABA/LAMA, LABA/ICS and LABA/LAMA/ICS combinations would help health care practitioners and societies to better position the place of LABA/LAMA combinations in the armamentarium of COPD therapies.

Contributors YO and STS conceived the study and were responsible for the data search and extraction. SD advised on the choice of Bayesian models, created the binomial-cloglog model and conducted the analyses on exacerbation outcomes. YO produced the figures and all authors contributed to the writing of the manuscript.

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Competing interests: None.

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FIGURE LEGENDS

Figure 1. Flow of study selection.

Figure 2. Diagram displaying the network of 4 arms involved in the Bayesian analysis. The links between nodes are used to indicate a direct comparison between pairs of treatments. The numbers shown along the link lines indicate the number of trials comparing pairs of treatments head-to-head. Abbreviations: LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

Figure 3. Summary effects of LABA/LAMA combination versus comparators on changes in trough FEV1 at 3, 6, and 12 months. Note: Mean difference in liters (95% credible interval) Abbreviations: LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

Figure 4. Summary effects of LABA/LAMA combination versus comparators on changes in (A) St. George's Respiratory Questionnaire and (B) Transition Dyspnea Index at 3 and 6 months. Note: Mean difference (95% credible interval). Abbreviations: LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

Figure 5. Summary effects of LABA/LAMA combination versus comparators on proportion of SGRQ and TDI responders at 6 months. Note: Odds ratio (95% credible interval). A responder was defined as a subject with an improvement of at least four units in SGRQ total score or one unit in TDI score. Abbreviations: LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist; SGRQ=St. George's Respiratory Questionnaire; TDI=Transition Dyspnea Index.

Figure 6. Summary effects of LABA/LAMA combination versus comparators on COPD exacerbations. Note: Hazard ratio (95% credible interval). Abbreviations: LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

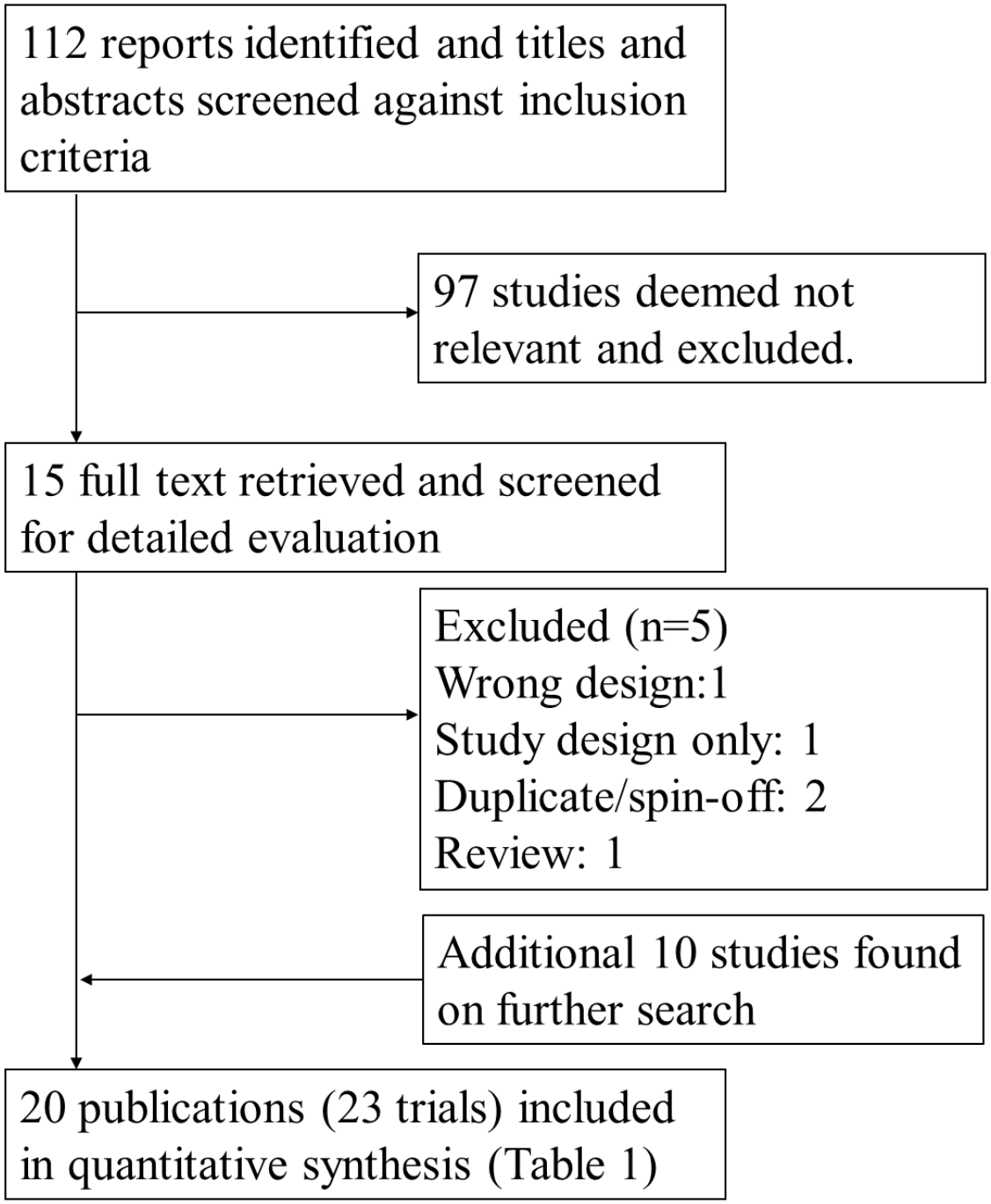
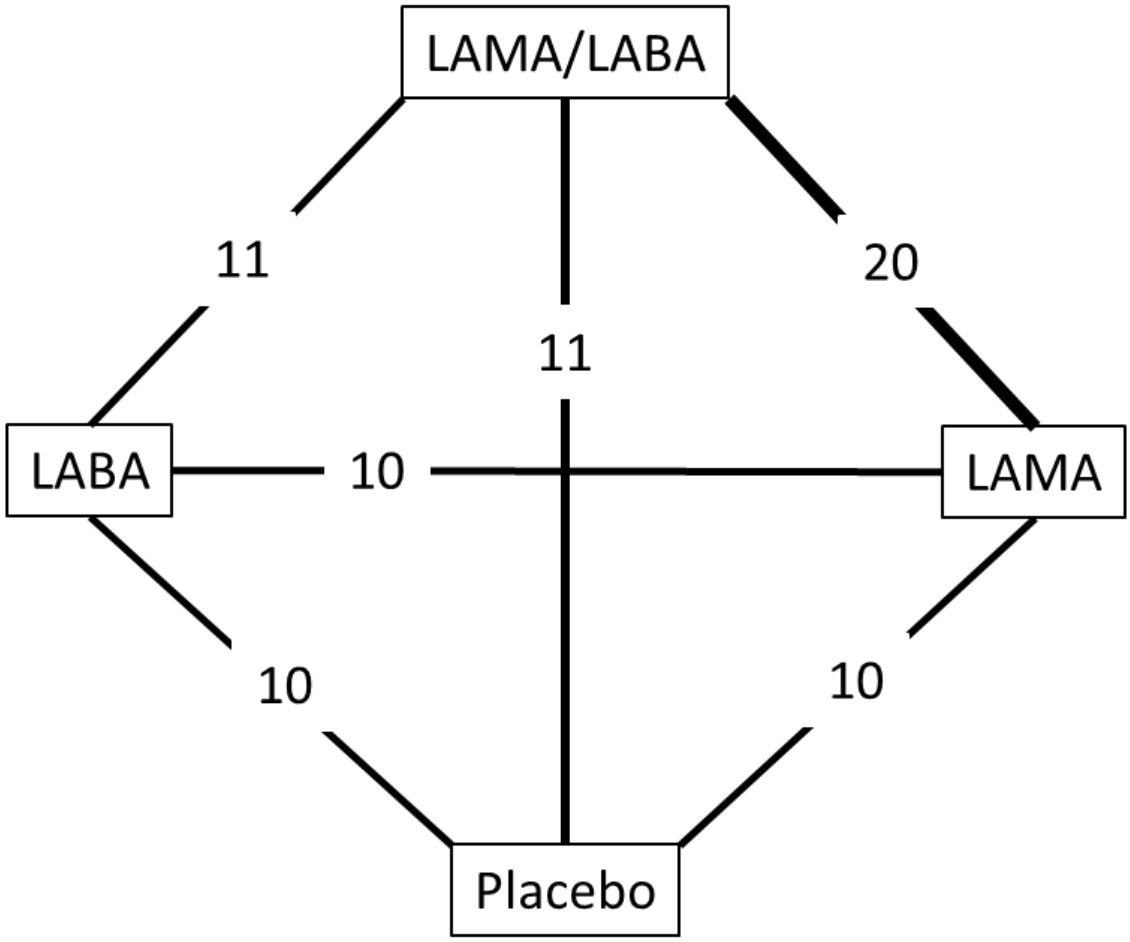


Figure 1 Flow of study selection.



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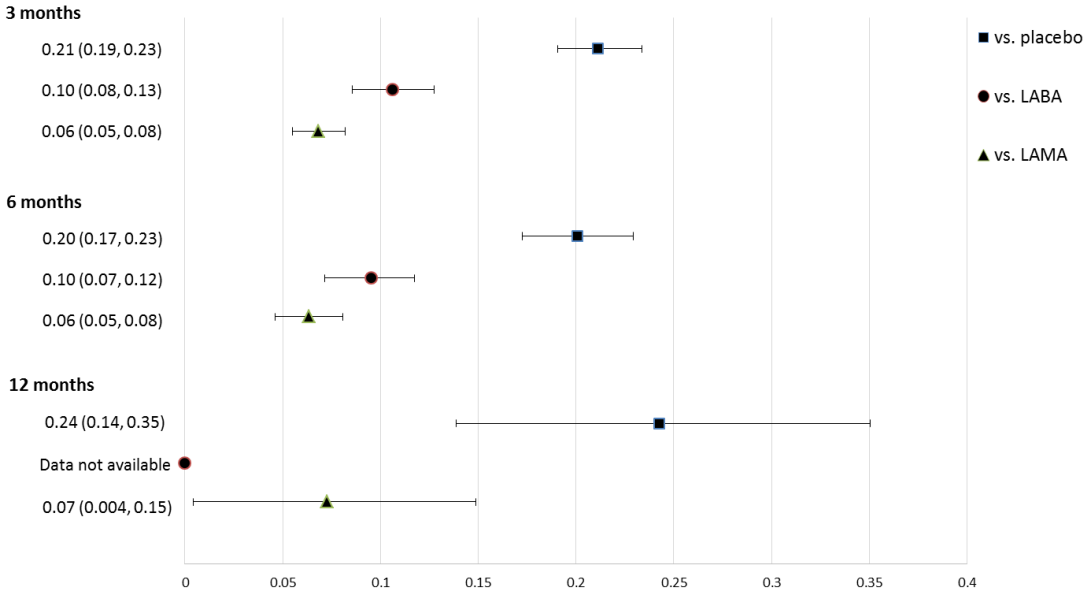
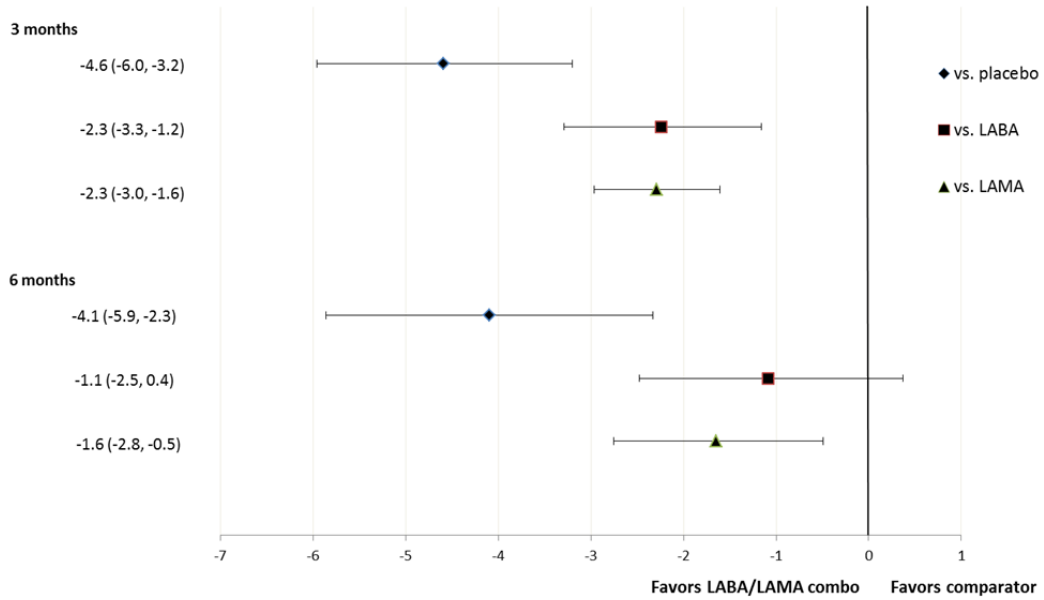
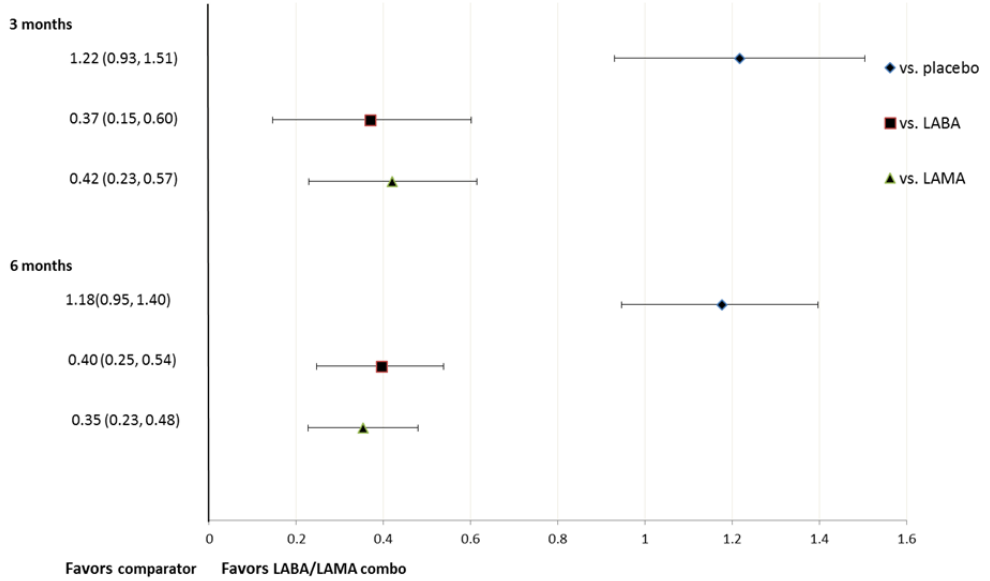


Figure 3. Summary effects of LABA/LAMA combination versus comparators on changes in trough FEV1 at 3, 6, and 12 months. Note: Difference in change from baseline in liters (95% credible interval) Abbreviations: LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.

A Changes from baseline in St. George's Respiratory Questionnaire



B Transition Dyspnea Index



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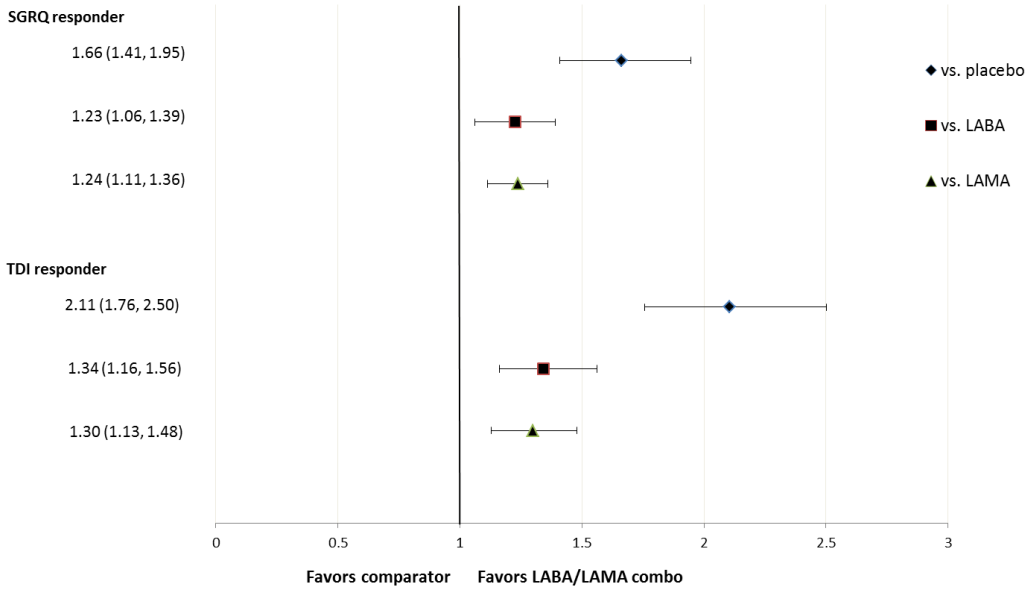

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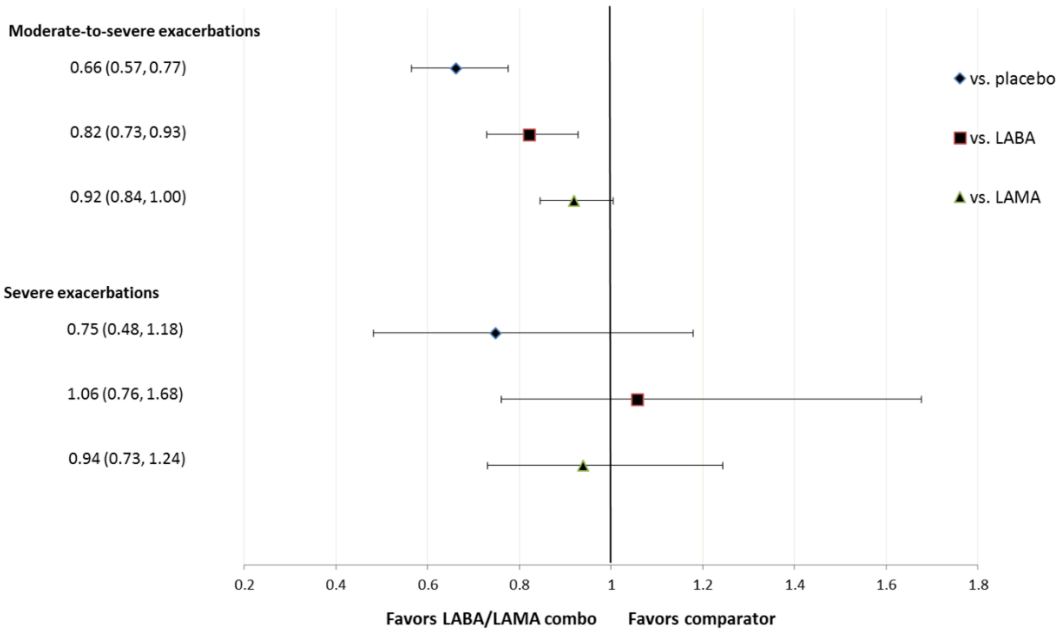

Figure 6. Summary effects of LABA/LAMA combination versus comparators on COPD exacerbations. Note: Hazard ratio (95% credible interval). Abbreviations: LABA= long-acting beta-agonist; LAMA= long-acting muscarinic antagonist.